

ORIGINAL ARTICLE

The potential epidemiological impact of a genital herpes vaccine for women

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Background: In two phase III vaccine trials immunisation of women previously uninfected by herpes simplex virus provided protection against genital herpes disease. In deciding policy, an evaluation of the epidemiological impact of the partial protection provided by the vaccine should be considered.

Methods: A sex and sexual activity stratified deterministic differential and partial differential equation model of the natural history of herpes simplex virus type 2 (HSV-2) and the impact of vaccination is developed and analysed. To explore the role of vaccination, the pattern of viral shedding and the transmission of infection during sexual acts within sexual partnerships are described.

Results: Using literature derived estimates of parameter values and assuming efficacy in only 40% of women the impact of the vaccine depends on assumptions made about its action. The vaccine has a limited impact if it only prevents disease but a more substantial impact if it reduces asymptomatic viral shedding, which it could do indirectly by preventing infection or directly by modifying the biology of the infection. Concern over the implications of a vaccine that prevents disease but has no impact on viral shedding was addressed in a worst case scenario. Here there is a modest increase in the incidence of infection in both men and women but an increase in disease prevalence in men alone, since the virus directly protects some women from disease.

Conclusions: Results suggest that a herpes vaccine should be used universally and that a vaccine that only protects HSV-1–/2– women can paradoxically have a significant epidemiological impact, the scale of which depends upon changes in patterns of viral shedding.

Beyond individual benefits, the public health significance of a new product should be considered. Historically, decisions about the use of vaccines with universally high efficacy have been relatively straightforward. However, as vaccine targets become more ambitious vaccine efficacy is likely to be less clear cut, and careful analysis is necessary to determine their potential population level effectiveness. Mathematical models provide a tool to describe precisely the assumptions made about the transmission dynamics of an infectious disease, and the potential impact of interventions.¹ The results of two phase III trials of an adjuvanted recombinant gD₂ vaccine reported by Stanberry and colleagues² provide a prime example of where the development and analysis of a mathematical model can inform the development of policy.

In stratified statistical analyses the vaccine generated significant protection against genital herpes disease and a convincing trend towards protection from infection with HSV-2, but only in herpes simplex virus (HSV) seronegative women. The vaccine provided no protection in men. Nor was there an indication of protection in women with previous HSV-1 infection who were HSV-2 seronegative (HSV-1+/2–). To explore the potential impact of a vaccine with this limited user profile and efficacy we used a mathematical model of the transmission dynamics of HSV-2 based on studies of the natural history and transmission of the virus. Our aim was, in part, to explore scenarios consistent with the observed efficacy of the vaccine to identify further information required from efficacy trials and to provide a framework for further analyses of the cost effectiveness of HSV control by vaccination.

METHODS

A mathematical model was developed that represents the observed natural history of HSV-2 infection. On infection a

fraction, depending upon sex and previous HSV-1 infection, develop primary disease,³ during which virus becomes latent. Both those with and without primary disease experience disease recurrences and episodes of asymptomatic shedding of virus.⁴ The rate of recurrence decreases over time⁵ as does the rate of asymptomatic viral shedding.⁶ Asymptomatic episodes are more frequent but of shorter duration than symptomatic recurrence.⁴ The mean duration of primary disease is longer than recurrences but appears to have declined,^{7,8} perhaps as a result of antiviral therapy. The model representing this natural history is illustrated in figure 1A and a technical appendix describing model equations and the assignment of parameter values is available on the *STI* website (www.stijournal.com/supplemental). The decline in recurrences is most reliably described for the first few years and is consistent with a number of functions, illustrated in figure 1B. These functions were explored in simulations but found not to greatly influence model results. In what follows a linear decline to no episodes after 8 years is assumed because it is numerically most tractable. Providing a longer tail to the duration of shedding would be more consistent with some observations, but its inclusion would potentially bias results in the absence of changing patterns of sexual activity with age, which are not included in this model.

In addition to stratification according to HSV-2 infection and disease, the model population was divided according to sex, sexual activity, and previous HSV-1 infection. People are assumed to be either HSV-1 seronegative or HSV-1 seropositive on entry to the sexually active population and to remain with their initial HSV-1 status. The model is fully defined in the appendix (on the *STI* website). The risk a susceptible person has of acquiring infection depends upon their rate of sexual partner change, their choice of sexual partners, and the proportion of the

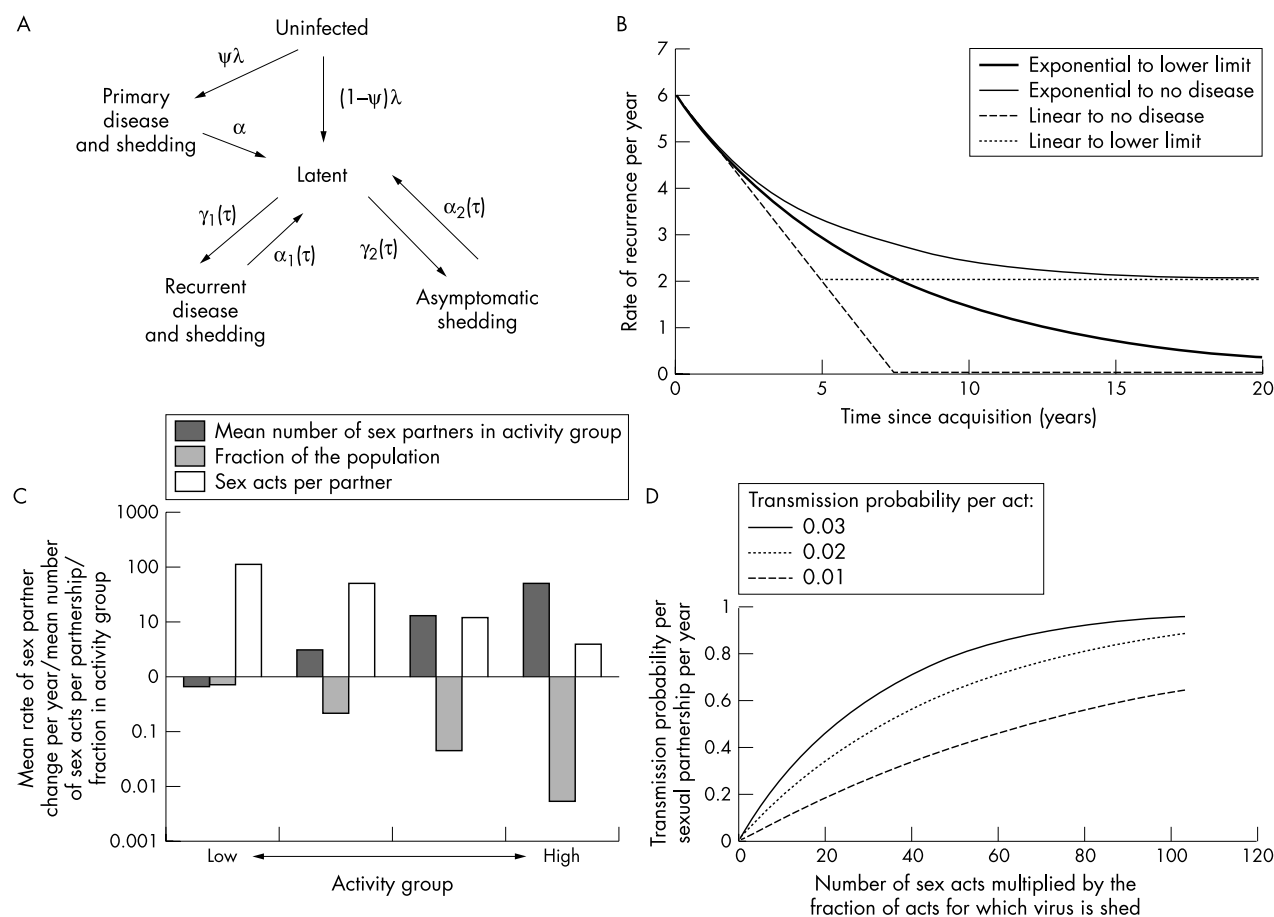


Figure 1 The natural history of herpes and patterns of risk behaviour represented in the model. (A) Possible states with respect to infection and disease and the rates of flow between these categories. (B) The four functions explored for the mean rate of recurrent episodes as a function of time since infection. (C) Distribution of the population with respect to rates of sexual partner change and number of sexual acts per partner. Values are derived from reported behaviour in a random sample of the US population¹¹ and patients with gonorrhoea in sexually transmitted disease clinics.¹² (D) The relation between the number of unprotected sex acts where virus is shed and the transmission probability per partnership of HSV-2.

partner pool infected. Such a framework is common to many models of the epidemiology of sexually transmitted diseases.⁹ Additionally, the likelihood of infection is dependent on the number of unprotected sex acts per year within partnerships where virus is being shed.¹⁰ The distribution of the population into sexual activity groups, defined according to rates of sexual partner change, and the frequency of sex acts of a partnership from a similar or lower activity group is illustrated in figure 1C.^{11 12} A binomial model is used to calculate the per partnership transmission probability based upon a risk per unprotected act during which virus is being shed (fig 1D). The number of such acts depends upon the fraction of time partners are shedding virus and the number of unprotected acts per partner. Those with many sex partners are assumed to have fewer acts per partner.¹³ Transmission probabilities generating the observed US prevalence were used.¹⁴ This model structure allows alterations in the frequency of disease recurrences and asymptomatic shedding episodes caused by vaccination to influence transmission.

The vaccine trial results are consistent with a number of interpretations. It is not discernable whether the vaccine offers partial protection from infection or disease in all HSV-1–/2– women or full protection in a fraction,¹⁵ except in as much as the end point was any disease as opposed to a reduced incidence of disease. For simplicity we assume that a fraction of the population is protected from all challenges and

a further fraction from all disease events. The two combine to provide the observed efficacy of protection from disease. We make a number of different assumptions about the impact of the vaccine on the relation between infection, disease, and shedding of virus:

- Disease alone is prevented (that is, symptomatic viral shedding is replaced by asymptomatic shedding). Because disease symptoms are assumed to decrease the likelihood of sex then the risks of transmission increase
- Disease episodes are prevented and the viral shedding that accompanies symptoms is no longer present, but asymptomatic episodes occur at the original rate
- Prevention of disease is synonymous with prevention of viral shedding and all episodes of viral shedding are prevented, but infection is not prevented
- The vaccine prevents infection but has no impact on disease or viral shedding in those infected. It should be noted that the 95% confidence intervals for the efficacy of the vaccine in preventing infection include the estimate of efficacy in protection against disease
- The vaccine prevents infection in some and disease and the viral shedding that accompanies symptoms in others
- The vaccine prevents infection in some, and disease and asymptomatic viral shedding in those who acquire infection but do not suffer disease.

All of the above assumptions are consistent with the results of the trial.

It is assumed that vaccine uptake increases linearly over the first 5 years to a maximum coverage of 50% of those commencing sexual activity, and 5% per year of those remaining. Over the lifetime of those at risk this will lead to a high fraction receiving vaccine at some stage during their life (after a years of sexual activity $0.5 + 0.5(1 - e^{-0.05a})$ of each cohort will have received vaccine). Except where explicitly stated, vaccine is assumed to only work in HSV-1-/2- women. A high HSV-1 seroprevalence of 60% is assumed in line with studies of 15 and 16 year olds in the US population.¹⁶

RESULTS

When vaccination perturbs the system, transient behaviour occurs over a time scale commensurate with the extremely long duration of infection (fig 2). In this best case scenario, the vaccine is assumed to cause a 42% reduction in the risk of infection and a further reduction in the risk of disease and asymptomatic viral shedding so that overall the reduced risk of disease is 73%. There is a gradual monotonic decline in the prevalence of infection (fig 2A), as those already infected leave the population, following on from a reduced incidence of new infections. This decline in the incidence of infection is more rapid, but still takes 20 or so years to be fully realised (fig 2B). Susceptible numbers slowly build up, leading to a slight rebound in incidence, before the system settles at a new equilibrium. Reductions in the prevalence of disease are associated with reductions in prevalence of infection, but correlate best with the reduction in incidence since primary disease, the most frequent recurrences, and the greatest risk of neonatal infection are all associated with incident infection (fig 2C).

The impact of a vaccine across the population depends upon its properties. Figure 3 shows the incidence of infections and the prevalence of disease for men and women. When the vaccine prevents disease and the viral shedding associated with disease, but does not prevent infection or asymptomatic viral shedding, then the only marked impact is a reduction in disease in women, the direct action of the

vaccine. When the vaccine reduces the risk of infection by 42.6% in HSV-1-/2- women alone, it causes a reduction in the incidence of infection and disease. The impact on infection and disease in the unvaccinated male population is of a similar order of magnitude, demonstrating the importance of indirect as well as direct effects of vaccine programmes. If a further reduction in disease and all viral shedding is added to the reduction in susceptibility, it has pronounced additional benefits on the incidence of infection and disease in both men and women.

The percentage reductions in the prevalence of disease and incidence of infection in men and women after 25 years of full vaccine uptake are presented in figure 4. The worst case scenario is a vaccine that prevents disease but not viral shedding and hence increases infections in the population (assuming no protection from infection), leads to a slight increase in the incidence of infection (of less than 5%) in men and women, and a slight increase in disease prevalence in men. In women the increase in infection is outweighed by the reduction in the risk of disease. A vaccine that reduces disease and asymptomatic viral shedding in women leads to greater reductions in disease among women than men, but infection is reduced more in men than women; whereas a vaccine that protects only against infection in women reduces infection more in women than men. When the two kinds of protection are combined the reduction in disease is always greater in women, but the impact on infection in the two sexes is balanced.

There are potential cost savings in STD control from targeting measures at those most likely to acquire and transmit infection. However, reaching those with the highest risk of acquiring and transmitting infection may be difficult, since such individuals may have lifestyles that put them out of the reach of vaccination programmes. We explored targeting with the sexual activity group as a marker of risk (fig 5A). Those with the most sex partners were assumed to have the "highest risk." Our results indicate that this is not the appropriate measure of risk of acquiring and transmitting infection. A combination of the number of sex partners and the number of sex acts would be more appropriate. To have a pronounced impact the bulk of the population who have

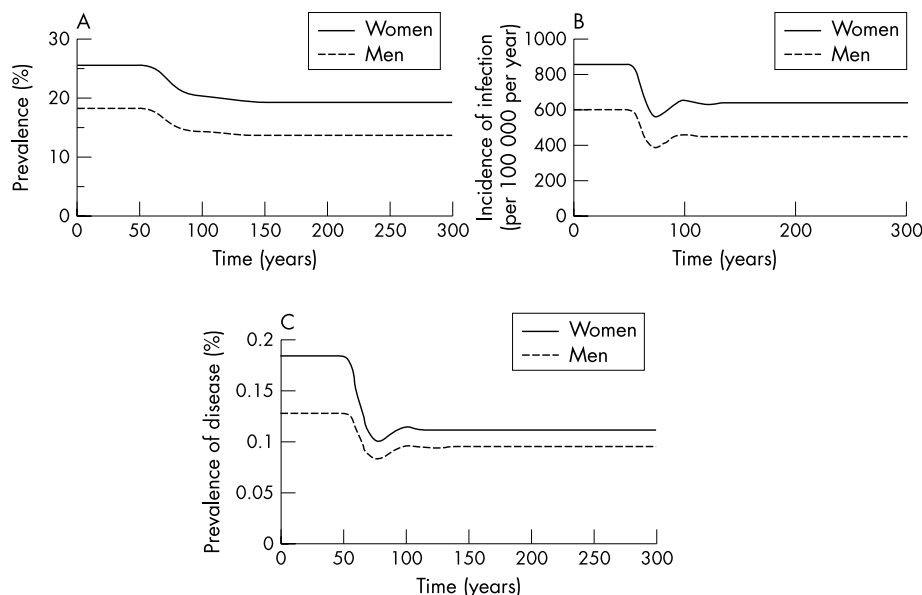


Figure 2 The modelled transient and long term impact of a vaccine introduced over years 50–55 that causes a 42% reduction in the risk of infection and a further reduction in the risk of disease so that overall the reduced risk of disease is 73%. Before the introduction HSV-2 is assumed to be at steady state. (A) The prevalence of HSV-2 in men and women. (B) The incidence of HSV-2 infections in men and women. (C) The prevalence of disease (that is, the proportion of the population with genital ulcers with a HSV-2 aetiology).

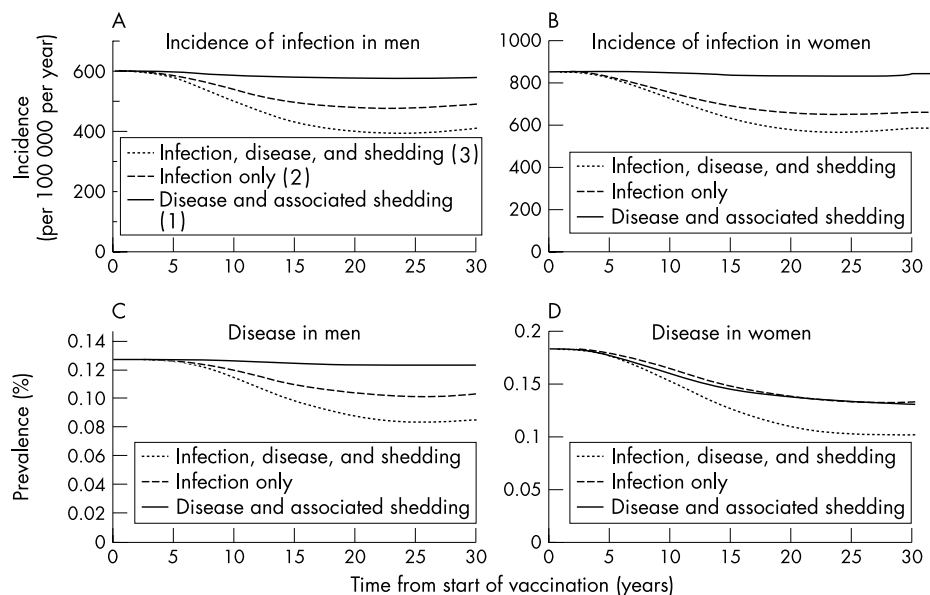


Figure 3 The transient impact of a vaccine with observed efficacy for three sets of assumptions about the behaviour of the vaccine: (1) that it prevents disease (73% efficacy) and the episodes of viral shedding that would normally accompany disease episodes (that is, asymptomatic viral shedding continues even those who are protected from disease by the vaccine); (2) that the vaccine provides a 42% efficacy in protecting against infection, without any protection from disease or viral shedding beyond this; (3) that the vaccine provides a 42% protection from infection and an additional protection from disease and asymptomatic viral shedding to generate a 73% protection in total.

“moderate” turnover in sex partners have to be vaccinated. This is different from what might be expected for bacterial STIs where targeting can be beneficial because they have a

shorter duration and higher per act transmission probability. Targeting to those with many sex partners forgoes most of the benefits of vaccination. Likewise, missing those with the

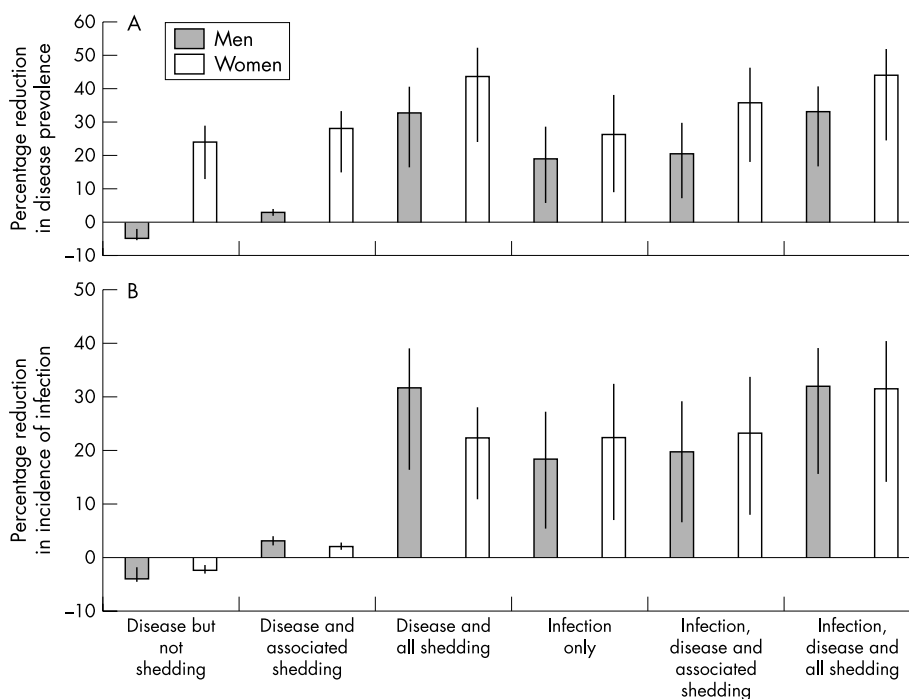


Figure 4 The percentage reduction in (A) the prevalence of genital HSV-2 disease and (B) the incidence of genital HSV-2 infection among men and women, after 30 years of vaccine use, for a range of vaccine properties with efficacies derived from the combined results of the HSV vaccine trials,² which showed an efficacy for protection from disease of 73 (95% CI 39 to 88) and potentially protection from infection of 42 (13 to 62) (pooled results). From left to right: (1) a vaccine that only ameliorates disease (73% efficacy), where disease episodes are replaced by asymptomatic viral shedding; (2) a vaccine which prevents disease and the periods of viral shedding that accompany disease (73% efficacy); (3) a vaccine which prevents disease and asymptomatic viral shedding (73% efficacy) without preventing infection; (4) a vaccine which prevents infection only (with 42.6% efficacy); (5) a vaccine that prevents infection (42% efficacy) and additional disease (up to 73% efficacy), but only prevents the asymptomatic shedding events that would have occurred along with disease; (6) a vaccine that prevents infection and additional disease and asymptomatic shedding. In all cases the vaccine only works in the 40% of women who are HSV-1 –/2–. The error bars are results when the 95% confidence intervals from the pooled vaccine trials results are used to parameterise the model.

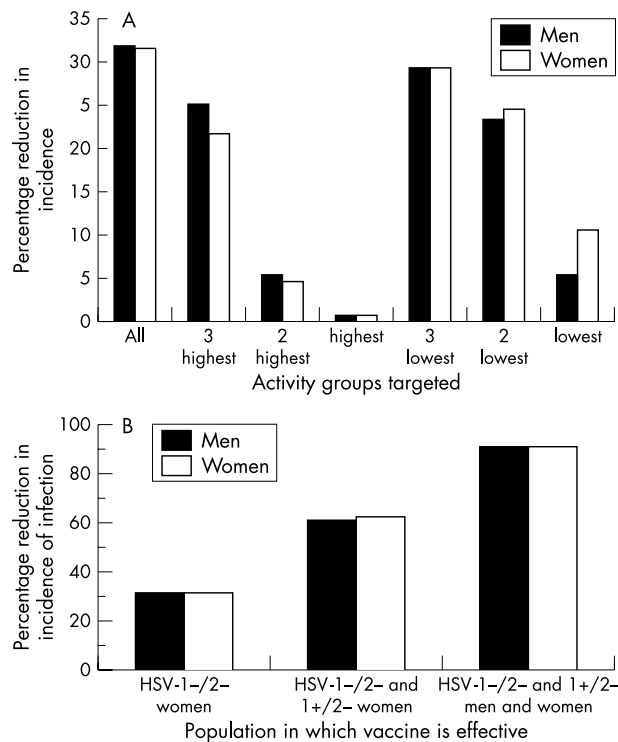


Figure 5 The percentage reduction in the incidence of genital HSV-2 infection after 30 years of use of a vaccine that prevents infection (42.6% efficacy) and additionally disease and asymptomatic viral shedding (total efficacy 72.8%). (A) Different targeting strategies—that is, restricting the activity groups, defined according to number of sex partners, receiving the vaccine. (B) Different efficacy profiles including a vaccine that only works in HSV-1-/2- women, that works in all women and that works in all men and women.

highest number of partners does not greatly undermine the success of the vaccination programme.

The impact of restricting vaccination to HSV-1-/2- women is illustrated in figure 5B, where, assuming the same efficacy, the limited use of vaccine is compared with vaccines used in all women and in all men and women. A single sex vaccine is almost as successful as a vaccine used in both sexes.

DISCUSSION

This modelling exercise indicates that a vaccine only protecting HSV-1-/2- women can have a substantial impact on genital herpes epidemiology. Indeed, the vaccine could more than offset the disturbing increase in the prevalence of HSV-2 infection observed between rounds of the NHANES survey of herpes virus prevalence.¹³ What explains this result? A vaccine that reduces the risk of infection moves susceptible people into an immune class decreasing the effective reproductive number, which in a homogeneous population would be expected to cause a linear decrease in the endemic prevalence of infection. Alternatively, when a vaccine reduces transmissibility it reduces the basic reproductive number where the decline increases as the value of the basic reproductive number approaches one.¹⁷ The declines predicted to follow a reduction in susceptibility or a reduction in transmissibility, suggest that the basic reproductive number of HSV-2 is low. An endemic prevalence of HSV-2 of 25% would be consistent with a reproductive number of $1\frac{1}{3}$ in a homogeneous population (based on the relation: prevalence = $1 - (1/R_0)$).¹⁷ Normally for STDs heterogeneity in risk of acquisition and transmission allows infection to saturate in a high activity section of the population, so that a small

fraction of the population has a high reproductive number and the bulk of the population has a very low reproductive number. Genital herpes risk is probably less heterogeneous, where a large fraction of the population has a moderate risk through a few sex partners with many sex acts per partner. With a widespread but low reproductive potential, small alterations in susceptibility or transmissibility for HSV-2 are translated into significant changes in incidence. This distribution of risk also explains the results of targeted vaccine use. Most of the impact of the vaccine results from protection of the large proportion of the population with a few sexual partners rather than those with very many sexual partners but few acts per partner. If an HSV-2 vaccine is to be used it should be used almost universally.

An important, if commonsense, conclusion is that protection of one sex (that is, women) from infection with a sexually transmitted disease also protects the other sex (that is, men) from heterosexual transmission. This would of course not extend to protecting men who have sex with men. The failure of the vaccine to protect HSV-1+/2- women is more significant than its failure to protect men. We assume a high HSV-1 prevalence in those vaccinated, which would be reduced with an earlier age of vaccination. Previous HSV-1 infection was assumed to ameliorate HSV-2 associated disease, but not alter the risk of acquiring HSV-2 infection or asymptomatic viral shedding. Either of these effects would increase the importance of those who are HSV-1 uninfected in the epidemiology of HSV-2 and enhance the impact of the vaccine.

The model results are dominated by the assumptions about the importance of asymptomatic shedding of virus in HSV-2 transmission. The fact that a vaccine which reduces disease but increases transmission is unlikely to increase the net burden of disease stems from the pre-existing dominance of asymptomatic viral shedding. However, this assumption also reduces the epidemiological impact of preventing viral shedding during episodes of disease. Current observations suggest that HSV-2 transmission is dominated by asymptomatic viral shedding.^{6, 18, 19} Hence, the impact of vaccination on asymptomatic viral shedding, either through preventing infection altogether or altering the course of infections, should be key to its public health function.

The perverse outcome of an increase in transmission is only found if we assume that those with disease reduce the frequency of unprotected sexual acts. The behaviour of the population in the vaccine trial² suggests that even when aware of infection and counselled to reduce risk behaviours this effect is not strong. Hence we may have erred on the side of caution in our analysis. However, if disease prompts healthcare seeking behaviour and there is a policy of use of antivirals to suppress viral shedding²⁰ then reductions in disease caused by vaccination could undermine such interventions but to have a major impact such interventions should screen for asymptomatic infections.²¹ In developing vaccination policy it will be important to consider the interactions between different interventions and to maximise any potential synergies.

To explore the cost effectiveness and cost benefits to be derived from the vaccine the model presented here requires further developments. Our results are based on a limited exploration of the behavioural and biological parameter space rather than a full sensitivity analysis. Such an analysis is required of future work with more tractable simpler models. The major adverse consequences of genital herpes are the risk of neonatal infection and the increased susceptibility and transmissibility of HIV. The decline in HSV-2 incidence achieved by the vaccine in this model provides some indication of what could be achieved in reducing neonatal herpes and HIV incidence, but a closer focus on the patterns of the

Key messages

- A vaccine against genital herpes which only works in women who are HSV-1–/2– can have a substantial impact on genital herpes epidemiology
- The impact extends from women to men
- The magnitude of the impact of genital herpes vaccine depends on whether it prevents asymptomatic shedding which can occur in two ways:
 - Prevention of disease is likely to correlate with prevention of asymptomatic shedding
 - Prevention of infection implicitly prevents asymptomatic shedding
- The impact of previous HSV-1 infection on the risk of HSV-2 infection is an important mediator of the vaccine's action

different diseases will be necessary in future research. A key development will be the introduction of age structure. This will allow the dynamics of HSV-1 to be incorporated along with age specific fertility rate in order to calculate the impact of the vaccine on neonatal herpes. Further models should also include the concomitant spread of HSV-2 and HIV.

CONTRIBUTORS

GG, TD, GD, and MS contributed to the design of the study, decided on analyses, and the drafting of the manuscript; GG developed the mathematical description, wrote the computer program to numerically solve the model, and carried out the analyses.



A technical appendix is available on the STI website (www.stijournal.com/supplemental)

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